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| APPLICATION NO.   | FILING DATE | FIRST NAMED INVENTOR   | ATTORNEY DOCKET NO.           | CONFIRMATION NO.       |
|---|-------------|------------------------|-------------------------------|------------------------|
| 10/538,499  | 08/03/2006  | Christopher John Burns | 415852000800                  | 7053                   |
| 25225 7590 10/15/2009<br>MORRISON & FOERSTER LLP<br>12531 HIGH BLUFF DRIVE<br>SUITE 100<br>SAN DIEGO, CA 92130-2040 |             |                        | EXAMINER<br>WILLIS, DOUGLAS M |                        |
|   |             |                        | ART UNIT<br>1624              | PAPER NUMBER           |
|   |             |                        | MAIL DATE<br>10/15/2009       | DELIVERY MODE<br>PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                                      |                                     |  |
|------------------------------|--------------------------------------|-------------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/538,499 | <b>Applicant(s)</b><br>BURNS ET AL. |  |
|                              | <b>Examiner</b><br>DOUGLAS M. WILLIS | <b>Art Unit</b><br>1624             |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 15-17 is/are pending in the application.
- 4a) Of the above claim(s) 11-13 and 15-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>07-21-05; 11-26-08</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Status of the Claims***

Claims 1-13 and 15-17 are pending in the current application. According to the *Amendments to the Claims*, filed September 23, 2009, claims 1, 2, 9-11, 13 and 15 were amended, claim 14 was cancelled and claims 16 and 17 were added. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/AU2003/001661, filed December 11, 2003, which claims priority under 35 U.S.C. § 119(e) to US Provisional Application No. 60/483,399, filed June 26, 2003, and under 35 U.S.C. § 119(a-d) to AU 2002953255, filed December 11, 2002.

### ***Status of Priority***

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 119(a-d) and 35 U.S.C. § 119(e) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(a-d) and 35 U.S.C. § 119(e) as follows:

The later-filed application must be an application for a patent, for an invention which is also disclosed in the prior applications (the provisional and foreign applications). The disclosure of the invention in the parent application and in the later-filed applications must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. {See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994)}.

The disclosure of the prior-filed applications, US Provisional Application No. 60/483,399 and AU 2002953255, fail to provide adequate support or enablement in the manner provided by

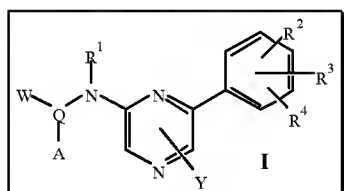
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the first paragraph of 35 U.S.C. § 112 for one or more claims of this application for the following reason: the specification in the instant application has been amended with respect to the scope of formula I, which now discloses *prodrugs* and an amended definition for  $R^{10}$ , and is no longer coextensive with that of either US Provisional Application No. 60/483,399 or AU 2002953255.

Consequently, since the specification of both US Provisional Application No. 60/483,399 and AU 2002953255 lack adequate support or enablement for one or more claims of the elected invention of Group I, as defined below in *Restrictions / Election of Species*, and in the manner provided by the first paragraph of 35 U.S.C. § 112, the first Office action on the merits of all relevant claims drawn to Group I will be prosecuted according to the earliest effective filing date afforded this invention, which is that of the parent application, filed December 11, 2003.

### ***Restrictions / Election of Species***

Applicant's provisional election of the following, without traverse, in the reply filed on



September 23, 2009, is acknowledged: a) Group I - claims 1-10; and b) substituted pyrazine of formula I - p. 57, Table 1, example 8, shown right below, and hereafter referred to as 2-methoxy-4-(6-(1-

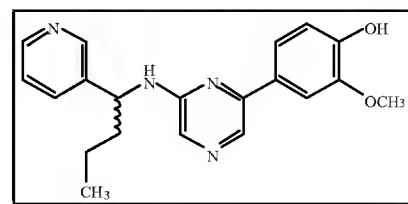
(pyridin-3-yl)butylamino)pyrazin-2-yl)phenol, where  $R^1 = -H$ ;  $R^2 = -OCH_3$ ;  $R^3 = -OH$ ;  $R^4 = -H$ ;

$Y = -H$ ;  $Q = -CH-$ ;  $W = -n-Pr$ ; and  $A = -pyridin-3-yl$ . Claims

1-3, 9 and 10 read on the elected species. Affirmation of this

election must be made by applicant in replying to this Office

action.



The requirement is still deemed proper and is therefore made FINAL.

Claims 11-13 and 15-17 were withdrawn from further consideration, pursuant to 37 CFR

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1.142(b), as being drawn to a nonelected or cancelled invention, there being no allowable generic or linking claim.

Thus, a first Office action and prosecution on the merits of claims 1-10 is contained within.

### ***Specification Objection - Disclosure***

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

### **Arrangement of the Specification**

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase *Not Applicable* should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
  - (1) Field of the Invention.
  - (2) Description of Related Art (including information disclosed under 37 CFR 1.97 and 1.98).
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825).

Applicant is advised to format the specification according to 37 CFR 1.77(b) above.

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Revisions should particularly include and/or address: a) bold-type formatting; and b) section heading (b). Appropriate correction may be required.

### ***Claim Objections***

Claims 1 and 2 are independently objected to because of the following informalities: a) *diastereomers* should be replaced with *stereoisomers*. Appropriate correction is required.

Claim 2 is further objected to because of the following informalities: *R*<sup>12</sup> should be replaced with *R*<sup>12</sup>, with respect to *R*<sup>2</sup>. Appropriate correction is required.

### ***Claim Rejections - 35 U.S.C. § 112, First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### ***Substituted pyrazines and pharmaceutical compositions of the formula I***

Claims 1-8 and 10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted pyrazines and pharmaceutical compositions of the formula I, where Y = -H or -C<sub>1-4</sub>alkyl; and no two of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, when located on adjacent carbon atoms, may be joined to form a ring system, does not reasonably provide enablement for substituted pyrazines and pharmaceutical compositions of the formula I, where Y ≠ -H or -C<sub>1-4</sub>alkyl; and two of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, when located on adjacent carbon atoms, form a ring system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Substituted pyrazines and pharmaceutical compositions of the formula I, where Y ≠ -H

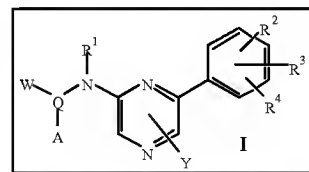
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or -C<sub>1-4</sub>alkyl; and two of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, when located on adjacent carbon atoms, form a ring system, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to make and/or use substituted pyrazines and pharmaceutical compositions of the formula I, where Y ≠ -H or -C<sub>1-4</sub>alkyl; and two of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, when located on adjacent carbon atoms, form a ring system.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. {See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986); and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)}.

The above factors, regarding the present invention, are summarized as follows:

- (a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted pyrazines and pharmaceutical compositions of the formula I, shown right;



- (b) *Nature of the invention* - the nature of the invention is evaluation of substituted pyrazines and pharmaceutical compositions of the formula I and the pharmacokinetic behavior of these substances in the human body as tubulin inhibitors;
- (c) *State of the prior art* - *Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with

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low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, 205);

- (d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's substituted pyrazines and pharmaceutical compositions of the formula I, where  $Y \neq -H$  or  $-C_{1-4}alkyl$ ; and two of  $R^2$ ,  $R^3$  and  $R^4$ , when located on adjacent carbon atoms, form a ring system, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;
- (e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (See *In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, which has extreme relevance to the synthesis of substituted pyrazines and pharmaceutical compositions of the formula I, where  $Y \neq -H$  or  $-C_{1-4}alkyl$ ; and two of  $R^2$ ,  $R^3$  and  $R^4$ , when located on adjacent carbon atoms, form a ring system (Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface):

*Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.*

*Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.*

*Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).*

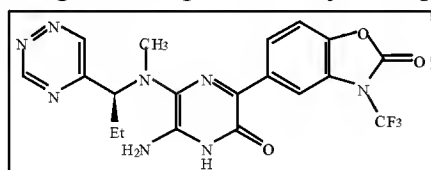
- (f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and/or using substituted pyrazines and pharmaceutical compositions of the formula I, where  $Y \neq -H$  or  $-C_{1-4}alkyl$ ; and two of  $R^2$ ,  $R^3$  and  $R^4$ , when located on adjacent carbon atoms, form a ring system;
- (g) *Existence of working examples* - applicant has provided sufficient guidance to make

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and/or use substituted pyrazines and pharmaceutical compositions of the formula I, where Y = -H or -C<sub>1-4</sub>alkyl; and no two of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, when located on adjacent carbon atoms, may be joined to form a ring system; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of substituted pyrazines and pharmaceutical compositions of the formula I, where Y ≠ -H or -C<sub>1-4</sub>alkyl; and two of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, when located on adjacent carbon atoms, form a ring system. The specification lacks working examples of substituted pyrazines and pharmaceutical compositions of the formula I, where Y ≠ -H or -C<sub>1-4</sub>alkyl; and two of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, when located on adjacent carbon atoms, form a ring system.

Within the specification, *specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Markush claims must be provided with support in the disclosure for each member of the Markush group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula. See MPEP § 608.01(p).*

- (h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, 205-213). Furthermore, it is unclear, based on the guidance provided by the specification, whether a substituted pyrazine of the



formula I, such as (S)-5-(6-((1-(1,2,4-triazin-5-yl)propyl)(methyl)amino)-5-amino-3-oxo-3,4-dihydropyrazin-2-yl)-3-(trifluoromethyl)-benzo[d]oxazol-2(3H)-one, shown to the left, is either synthetically feasible or possesses utility in the

human body as a tubulin inhibitor.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {See *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use

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the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and/or using substituted pyrazines and pharmaceutical compositions of the formula I, where  $Y \neq -H$  or  $-C_{1-4}alkyl$ ; and two of  $R^2$ ,  $R^3$  and  $R^4$ , when located on adjacent carbon atoms, form a ring system, is clearly justified.

***Hydrates, solvates and crystal forms of substituted pyrazines and pharmaceutical compositions of the formula I***

Claims 1-8 and 10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted pyrazines and pharmaceutical compositions of the formula I, does not reasonably provide enablement for *hydrates, solvates and crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. *Hydrates, solvates and crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I, as recited in claim 1, have not been adequately enabled in the specification to

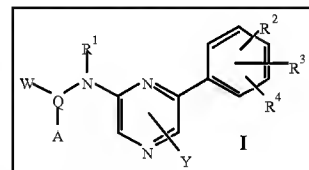
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allow any person having ordinary skill in the art, at the time this invention was made, to make and/or use *hydrates*, *solvates* and *crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. {See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986); and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)}.

The above factors, regarding the present invention, are summarized as follows:

- (a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted pyrazines and pharmaceutical compositions of the formula I, shown right, as well as the myriad of potential *hydrates*, *solvates* and *crystal forms* formulated from these substituted pyrazines and pharmaceutical compositions of the formula I, respectively;



- (b) *Nature of the invention* - the nature of the invention is evaluation of *hydrates*, *solvates* and/or *crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I and the pharmacokinetic behavior of these substances in the human body as tubulin inhibitors;
- (c) *State of the prior art - Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, 205);

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- (d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's *hydrates, solvates and/or crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;
- (e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (See *In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Vippagunta, et al. with respect to the synthesis of *hydrates and solvates* of substituted pyrazines and pharmaceutical compositions of the formula I (Vippagunta, et al. *Advanced Drug Delivery Reviews*, 48, **2001**, 18):

*Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates.*

Similarly, the following excerpt is taken from Chawla, et al. with respect to the synthesis of *crystal forms (polymorphs)* of substituted pyrazines and pharmaceutical compositions of the formula I (Chawla, et al. *Curr. Res. & Info. Pharm. Sci. (CRIPS)*, 5, 1, **2004**, 9-12):

*Polymorphism is the ability of a substance to exist in two or more crystalline phases that have different arrangement and/or conformation of molecules in the crystal lattice. However, they share a common form once they are in the solution phase. It can significantly affect the physiochemical, formulation and processing parameters, as well as the shelf life (stability) of the drug substance and excipients.*

*Polymorphism has contributed significant variability in product performance in pharmaceutical, chemical and food industry and continues to pose a challenge to pharmaceutical scientists in producing drugs of consistent quality. An inadvertent production of the 'wrong' polymorph at the crystallization stage or any transformations of one form to another during dosage form processing, storage and scale-up can result in pharmaceutical dosage forms which are either ineffective or toxic.*

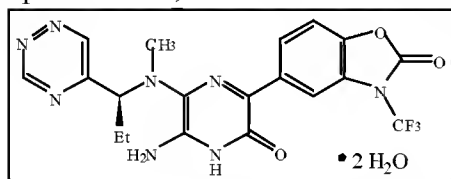
- (f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and/or using *hydrates, solvates and/or crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I;

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- (g) *Existence of working examples* - applicant has provided sufficient guidance to make and/or use substituted pyrazines and pharmaceutical compositions of the formula I; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of *hydrates, solvates* and/or *crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I. The specification lacks working examples of *hydrates, solvates* and *crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I.

Within the specification, *specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Markush claims must be provided with support in the disclosure for each member of the Markush group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula. See MPEP § 608.01(p).*

- (h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a *hydrate, solvate* and/or *crystal form* of a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, 205-213). Furthermore, it is unclear, based on the guidance provided by the specification, whether a solvate of a substituted pyrazine of the formula I, such as



(*S*)-5-(6-((1-(1,2,4-triazin-5-yl)propyl)(methyl-amino)-5-amino-3-oxo-3,4-dihydropyrazin-2-yl)-3-(trifluoromethyl)-benzo[*d*]oxazol-2(3*H*)-one dihydrate, shown to the left, is either synthetically feasible or possesses utility in the

human body as a tubulin inhibitor.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {See *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion

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reached by weighing all the above noted factual considerations. (See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and/or using *hydrates*, *solvates* and *crystal forms* of substituted pyrazines and pharmaceutical compositions of the formula I, is clearly justified.

***Claim Rejections - 35 U.S.C. § 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase *optionally substituted*, in claims 1 and 2, respectively, is a relative phrase which renders the claims indefinite. The phrase *optionally substituted* is not defined by the claims, the specification does not provide an adequate standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification fails to adequately define the phrase *optionally substituted*. Consequently, the *substituted* pyrazines and pharmaceutical compositions of the formula I have

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been rendered indefinite by the use of the phrase *optionally substituted*.

The examiner suggests removal of the phrase *optionally substituted* and providing discrete substituents for each occurrence where substituents are desired, to overcome this rejection.

Claims 1, 3-8 and 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation *Q is a bond...*, where *W* contains an incomplete valence. Claims are unduly speculative where they define only a portion of a molecule. Thus, since incomplete valences are not permitted in the structure of the substituted pyrazines of the formula I, an essential portion of the molecule is indefinite and one of ordinary skill in the art, would not be reasonably apprised of the scope of the substituted pyrazines of the formula I. {See *Ex parte Pedlow and Miner*, 90 USPQ 395 (Bd. Pat. App. & Int. 1951)}.

The examiner suggests clarifying the bonding scheme, with respect to *Q* and *W*, to overcome this rejection.

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation *a compound according to claim 1... wherein... Y is... NR<sup>12</sup>R<sup>13</sup>; and R<sup>12</sup> and R<sup>13</sup>... may be joined to form an optionally substituted 3-6 membered ring....* There is insufficient antecedent basis, in claim 1, for this limitation, with respect to the substituted pyrazines of the formula I. According to claim 1, *Y* is -NR<sup>22</sup>R<sup>23</sup>, and R<sup>22</sup> and R<sup>23</sup> are

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each independently *H* or *C<sub>1-4</sub>alkyl*, with respect to the substituted pyrazines of the formula I.

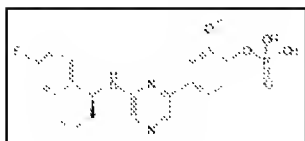
Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase *at least a portion* is a relative phrase which renders the claims indefinite. The phrase *at least a portion* is not defined by the claims, the specification does not provide an adequate standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification fails to adequately define the phrase *at least a portion*. Consequently, the substituted pyrazines and pharmaceutical compositions of the formula I have been rendered indefinite by the use of the phrase *at least a portion*.

The examiner suggests removal of the phrase *at least a portion* and providing discrete limitations for each occurrence where *a portion* is desired, to overcome this rejection.

Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the limitation *a compound according to claim 1... wherein the compound*



*is....* There is insufficient antecedent basis, in claim 1, for this limitation, with respect to the substituted pyrazine, shown to the left.

According to claim 1, the aforementioned species is not a substituted pyrazine of the formula I, but a *prodrug* thereof.

***Claim Rejections - 35 U.S.C. § 102***

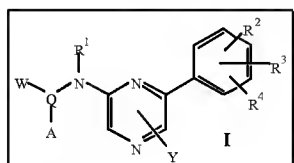
The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

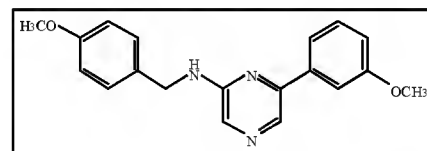
Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ding, et al. in *JACS*, 124(8), **2002**, 1594-1596.

The instant application recites substituted pyrazines of the formula I, shown to the left,



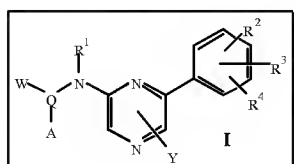
where  $R^1 = -H$ ;  $R^2 = -OC_{1-4}alkyl$ ;  $R^3 = -H$ ;  $R^4 = -H$ ;  $Y = -H$ ;  $Q = -C_{1-4}alkyl$ ;  $W = -H$ ; and  $A = -aryl$ , substituted with  $p-OC_{1-4}alkyl$ , as tubulin inhibitors.

Ding, et al. [*JACS*, 124(8), **2002**], as provided in the file and cited on the IDS, teaches substituted pyrazines of the formula I, shown to the right, where  $R^1 = -H$ ;  $R^2 = -OCH_3$ ;  $R^3 = -H$ ;  $R^4 = -H$ ;  $Y = -H$ ;  $Q = -CH_2$ ;  $W = -H$ ; and  $A = -Ph$ , substituted with  $p-OCH_3$ , as synthetic targets from kinase inhibitor scaffolds [p. 1596, Table 2, Entry 12].



Claims 1, 3-8 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Burns, et al. in WO 02/060492.

The instant application recites substituted pyrazines and pharmaceutical compositions of



the formula I, shown to the left, where  $R^1 = -H$ ;  $R^2 = -NR^8COR^9$ , wherein  $R^8 = -H$  and  $R^9 = -C_{1-4}alkyl$ ;  $R^3 = -H$ ;  $R^4 = -H$ ;  $Y = -H$ ;  $Q = -$

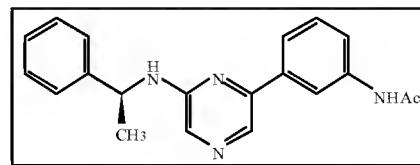
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C<sub>1-4</sub>alkyl; W = -C<sub>1-4</sub>alkyl; and A = -aryl, as tubulin inhibitors.

Burns, et al. (WO 02/060492), as provided in the file and cited on the IDS, teaches substituted pyrazines and pharmaceutical compositions of the

formula I, shown to the right, where R<sup>1</sup> = -H; R<sup>2</sup> = -

NR<sup>8</sup>COR<sup>9</sup>, wherein R<sup>8</sup> = -H and R<sup>9</sup> = -CH<sub>3</sub>; R<sup>3</sup> = -H; R<sup>4</sup> = -H;



Y = -H; Q = -CH-; W = -CH<sub>3</sub>; and A = -Ph, as protein kinase inhibitors [p. 38, Table 4, compound 20508; and pharmaceutical compositions - p. 17, lines 12-21].

Finally, although not explicitly discussed herein, applicant is advised to note that the Burns reference contains additional species that may anticipate the instantly recited substituted pyrazines of the formula I. Consequently, any amendments to the claims to overcome rejections rendered under 35 U.S.C. § 102 should address this reference as a whole and should not be limited to the species discussed or disclosed explicitly herein.

### ***Claim Rejections - Obviousness-type Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute), so as to prevent the unjustified or improper timewise extension of the *right to exclude* granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claims because the examined application claim is either anticipated by, or would have been obvious over, the reference claims. {See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In*

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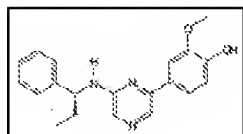
*re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969)}.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

***US Application No. 10/581,534***

Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10/581,534. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 in the copending application recites definitions for  $A$ ,  $Q$ ,  $W$ ,  $R^1$ ,  $R^2$  and  $Y$ , which provide overlapping subject matter with respect to the instant claims. For example, claim 1 of the copending application recites a method of treatment, comprising administering substituted pyrazines of the formula I, while claim 2 of the copending application recites a method of treatment, comprising administering substituted pyrazines of the formula I,



shown to the left, which are homologous, with respect to  $W$ , to those recited in claim 9 of the instant application.

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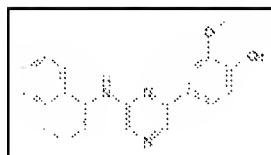
***US Application No. 11/367,248***

Claims 1-3 and 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 6-14 of copending Application No. 11/367,248. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 in the copending application recites definitions for  $A$ ,  $Q$ ,  $W$ ,  $R^1$ ,  $R^2$  and  $Y$ , which provide overlapping subject matter with respect to the instant claims. For example, claim 1 of the copending application recites a method of treatment, comprising administering substituted pyrazines of the formula I, as recited in claims 1 and 2, respectively, of the instant application.

The aforementioned are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

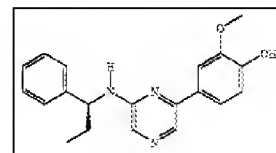
***US Patent No. 7,122,550***

Claims 1-10 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of *US 7,122,550*. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 9 of the



instant application recites a substituted pyrazine of the formula I, shown to the left, which is a homologous racemate, with

respect to  $W$ , of a substituted pyrazine recited in claim 9 of *US 7,122,550*, shown to the right above.

***Allowable Subject Matter***

No claims are allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DOUGLAS M WILLIS/  
Examiner, Art Unit 1624

/James O. Wilson/  
Supervisory Patent Examiner, AU 1624